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Androgens and Severe Insulin Resistance States: Basic and Clinical Aspects

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Abstract

Hyperandrogenism with or without polycystic ovary syndrome can be sustained by an extreme form of insulin resistance (IR), and is thus a secondary form of hyperandrogenism, which may be due to a defect in insulin signal transduction or in the adipose tissue. Severe IR due to adipose tissue dysfunction is the most frequent form, which may be the result of a deficiency in the adipose tissue, that is, the lipodystrophies, or to the unrestrained accumulation of adipose tissue. These forms are in some cases produced by a single-gene defect. The diagnosis remains predominantly clinical by examining patients in their underwear and looking out for clinical hallmarks, supported by biochemical biomarkers. Gene screening is necessary to corroborate the diagnosis of some forms. Clinicians who deal with hyperandrogenic disorders should be alerted to the forms that are secondary to severe IR, as they are not as uncommon as often imagined and frequently respond to tailored therapies.

How to Biochemically Suspect a Severe Insulin Resistance State

Although no formal biochemical definition of severe insulin resistance (IR) exists, there is general consensus that the following conditions are indicators: a fasting insulin value above 20.9 $\mu\text{U/mL}$ (150 pmol/L) and/or a peak insulin value on oral glucose tolerance testing above 209 $\mu\text{U/mL}$ (1,500 pmol/L) when diabetes is absent and a body mass index (BMI) below 30 kg/m^2 ; or an exogenous insulin requirement of above 3 U/kg of body weight per day when diabetes with absolute insulin deficiency is present in association

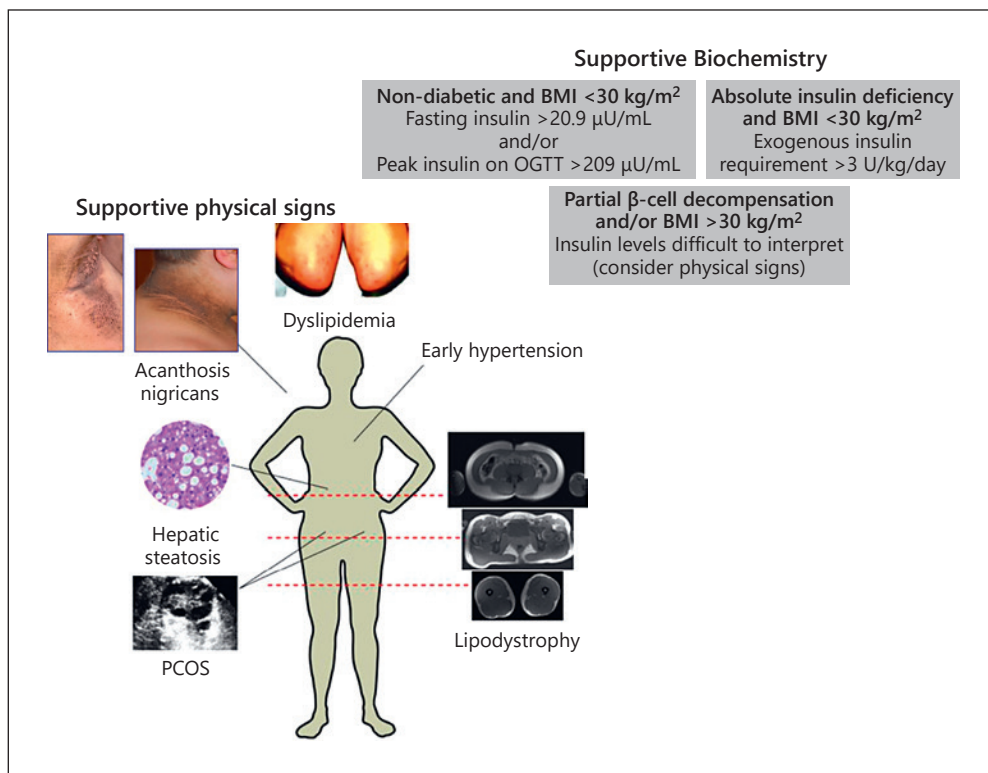


Fig. 1. Supportive clinical and biochemical aspects for severe insulin resistance (IR). BMI, body mass index; PCOS, polycystic ovary syndrome.

with a BMI below 30 kg/m² [1]. However, in patients with partial β-cell compensation and/or with a BMI above 30 kg/m², a diagnosis of severe IR is more difficult and should also include the clinical history and the presence of some physical signs (see the next section), although high c-peptide levels can help in the diagnosis in insulin-treated patients [1] (Fig. 1).

Severe IR States: Clinical Aspects

IR is usually a condition of “partial” IR, which means that only some tissues are insulin resistant, particularly those involved in the metabolic effects of insulin (skeletal and cardiac muscle and adipose tissue), whereas other tissues such as the pituitary, adrenal, ovary, the skin and to some extent the liver, maintain a level of insulin sensitivity. In IR states, insulin is thus unable either to regulate glucose homeostasis at the level of adipocytes, skeletal and cardiac muscle or to suppress hepatic glucose production and lipolysis at the level of the adipose tissue. This then results in an increase in blood glucose and in circu-

lating free fatty acid (FFA) levels [1]. On the other hand, before β -cell decompensation, the tissues that remain insulin-sensitive are exposed to the biological effects of exaggerated circulating insulin levels, which compensate IR.

Taken together, the above mechanisms lead to the most clinically important component of the manifestations of severe IR states, which are acanthosis nigricans, a severe combined dyslipidemia (high triglycerides and low HDL-cholesterol levels), sometimes complicated by eruptive xanthomata and episodes of acute pancreatitis, an unusually severe spectrum of fatty liver diseases, ranging from non-alcoholic fatty liver disease through steatohepatitis to advanced cirrhosis and rarely hepatocellular carcinoma, and early-onset hypertension and atherosclerotic diseases. In females, severe IR states are usually associated with clinical and/or biochemical hyperandrogenism and, possibly, with polycystic ovary syndrome (PCOS; Fig. 1).

Frequently there is also a lipodystrophic phenotype that may be generalized or, more frequently, partial. Interestingly, acanthosis nigricans and, in females, hyperandrogenism with or without PCOS, accompany almost all the forms of severe IR states, including the forms due to insulin receptor (INSR) defects. In the latter forms, however, there is no dyslipidemia, fatty liver disease, or early atherosclerosis, thus suggesting that some in vivo effects of insulin are not only INSR mediated [1].

Acanthosis nigricans can be considered the clinical marker of severe IR and of all the IR states in general. It is characterized by thickened, brown, velvety skin in flexures, often associated with skin tags or acrochordons. In the most severe cases, there may be perioral, periocular and buccal regions, even on planar surfaces (Fig. 1).

Severe IR States: How Many Causes Do We Actually Know?

For many years, the term “HAIR-AN” has been commonly used to identify the association between hyperandrogenism, severe IR and acanthosis nigricans. However, this is an imprecise, simplistic and overlapping definition of an extremely heterogeneous number of different forms of severe IR states associated with hyperandrogenism. Over time this term has thus been abandoned and replaced by mechanism-based classifications. Severe IR states are now usually classified in 2 categories: those disorders in which there is a primary defect in insulin signal transduction (Primary IR) and those in which severe IR is a consequence of adipose tissue dysfunction [2].

Primary IR can be then subdivided into the forms in which there is a defect at the level of the INSR, and the forms in which there is a signaling defect that is limited either to only some parts of the postreceptor signal transduction pathway or to some tissues [2]. The INSR spectrum of disorders includes those due to INSR autoantibodies and INSR mutations [2]. INSR autoantibodies act in various ways including direct binding-site inactivation, accelerated receptor degradation, or inhibition of conformational changes within the receptor after binding. Only a few mutations have been discovered that are involved in the defect of the signalling pathway downstream of the INSR. These consist of

a non-functional mutation in AKT2 encoding a critical serine/threonine kinase and a non-sense mutation in AS160 encoding for a GTPase-activating protein that forms the link between insulin signalling and glucose uptake by the GLUT4 transporters [2].

Adipose tissue dysfunction is the most frequent form of severe IR, which can be subdivided into a group with lipodystrophy, in which there is a deficiency in subcutaneous adipose tissue, and into another group in which the defect comprises an unrestrained accumulation of adipose tissue; it is therefore associated with severe obesity commonly due to hyperphagia [2]. Lipodystrophy can be generalized or partial, congenital or acquired [2].

A combination of linkage analysis and candidate gene screening has led to the identification of a list of genes associated with congenital lipodystrophies, which encode essential proteins for normal fat tissue development and/or function in humans. The genes implicated in the pathogenesis of congenital lipodystrophies can be categorized as being primarily involved in: the transcriptional regulation of adipocyte differentiation; fatty acid uptake; triacylglycerol (TAG) synthesis; and lipid droplet formation [3]. The genes involved in the alteration of adipocyte differentiation are the peroxisome proliferator activated receptor γ -PPARG, a member of the nuclear hormone receptor superfamily; LMNA, an encoding lamin A/C, which is a nuclear envelope protein with many cellular roles including chromatin and transcription factor binding and organization of the nuclear membrane and cytoskeleton; zinc metalloproteinase STE24 homologue-ZMPSTE24, which encodes a metalloproteinase essential for the processing of prelamin A to mature lamin A protein; and AKT2, a Ser/Thr kinase that is critical in the insulin-signaling cascade required for adipogenesis [4].

The 2 genes involved in the alteration in fatty acid uptake by adipocytes are (i) CAV1, which encodes caveolin-1; and (ii) PTRF, which encodes polymerase 1 and the transcript release factor, also called cavin-1, which are proteins that mediate caveolae formation or stabilization. Caveolae are specialised plasma membrane microdomains involved in fatty acid uptake, INSR recycling and GLUT4 organisation in adipocytes. The loss of these proteins likely disrupts adipose tissue function, both through impairment in the fatty acid uptake, and thus TAG synthesis, and, more speculatively, through the loss of insulin signalling into the cell.

AGPAT2 is the gene involved in the alteration in TAG synthesis, encoding the enzyme acylglycerol 3-phosphate O-acyltransferase 2, which is located in the endoplasmic reticulum and catalyses the conversion of lysophosphatidic acid to phosphatidic acid, a key step in the synthesis of triglycerides and glycerolphospholipids from glycerol-3-phosphate. Finally, the genes behind the alteration in lipid droplet formation are Berardinelli-Seip congenital lipodystrophy-BSCL2 or seipin, cell death-inducing DFFA-like effector C or CIDED, and Perilipin-PLIN1, each of which resides on the surface of the lipid droplet and regulates triglyceride mobilization.

Mutations in another 2 genes associated with inherited forms of lipodystrophies have recently been described: polymerase delta 1 or hormone-sensitive lipase [2, 5, 6].

Mutations in BSCL2, AGPAT2, CAV1, and PTRF cause congenital generalized lipodystrophies that are characterized by the nearly complete absence of subcutaneous adi-

pose tissue and consequently a generalized muscular appearance that is easily recognized at birth. On the other hand, mutations in LMNA, PPARG, PLIN1, CIDEC, ZMPSTE24, AKT2, polymerase delta 1 and hormone-sensitive lipase cause congenital partial lipodystrophies, which are always characterized by a loss of fat in the arms, legs, and buttocks, as well as loss of fat that typically starts during puberty and gradually gets worse [7]. The most frequent form of congenital partial lipodystrophy is due to missense mutations at the level of the LMNA gene, known as familial partial lipodystrophy (FPLD) type 2. FPLD type 2 is phenotypically characterized by the loss of fat in arms more prominently in the forearms and calves than in the upper arms and thighs, a variable and progressive loss of subcutaneous fat from the chest, and an abnormal gain of fat in the face and neck and intra-abdominal region.

Another quite frequently inherited variety of partial lipodystrophy is FPLD type 1 or Köbberling syndrome, where a polygenic or oligogenic pathogenesis has been suggested. The phenotype starts in childhood, and worsens with menopause and weight gain. Despite the apparent lipodystrophy in the lower limbs, which can be variable in the upper limbs, patients are frequently obese and have a notable accumulation of abdominal fat (including subcutaneous fat), and thus are usually diagnosed with android obesity [8, 9].

The acquired forms of lipodystrophies are phenotypically characterized by a defect in adipose tissue that affects the face, neck, thorax (in the partial forms), and also arms, legs, and sometimes the palms and soles (in the generalized form), but the abdomen is preserved and not in excess. In the partial forms, there may be a compensatory accumulation of adipose tissue in the glutea and legs. In acquired lipodystrophy, the fat loss may appear at any age depending on the time of appearance of the primary cause.

Clinicians who manage hyperandrogenism in females should be alerted to these forms as they are secondary to severe IR states and, therefore, usually benefit from tailored therapies.

Basic Mechanisms for the Association between Severe IR States and Hyperandrogenism

Insulin can produce hyperandrogenism in females with severe IR states by acting at the level of different tissues, which trigger the synthesis and peripheral actions of androgens (Table 1). Insulin enhances the pituitary response of LH to GnRH, finally stimulating ovarian LH-mediated androgen production [2]. At the ovarian level, insulin upregulates LH receptors, as well as type 1 IGF and hybrid insulin/type 1 IGF receptors, thus increasing the production of androgens, estrogens and progesterone by the granulosa and thecal cells. In addition, insulin directly increases ovarian androgen synthesis by stimulating cytochrome P450c17 α activity, a key enzyme in the biosynthesis of androgens, which has both 17 α -hydroxylase and 17,20-lyase activities [2]. Insulin also increases IGF-1 expression and downregulates IGF binding protein production in the ovary, leading to a local increase in free IGF-1 and IGF-2 levels that act on thecal cells to enhance androgen pro-

Table 1. Basic mechanisms for the association between severe insulin resistance states and hyperandrogenism in females

Effect of insulin excess	Effect of androgen excess
<i>Pituitary</i> <ul style="list-style-type: none"> – Enhances the effect of GnRH on LH 	<i>Adipose tissue</i> <ul style="list-style-type: none"> – Induces hypertrophy – Decreases insulin sensitivity – Increases visceral lipid accumulation
<i>Ovary</i> <ul style="list-style-type: none"> – Acts synergistically with LH to stimulate steroidogenesis – Upregulates LH receptors – Directly stimulates steroidogenesis – Upregulates type 1 IGF receptors or hybrid insulin/type 1 IGF receptors – Inhibits SHBG production – Inhibits IGFBP-1 production – Promotes polycystic ovarian morphology and anovulation 	<i>Skeletal muscle</i> <ul style="list-style-type: none"> – Decreases insulin sensitivity
<i>Adrenal</i> <ul style="list-style-type: none"> – Stimulates androgen production 	
<i>Liver</i> <ul style="list-style-type: none"> – Inhibits SHBG production – Inhibits IGFBP-1 production 	

duction [2]. Insulin may also stimulate adrenal androgen production through a direct effect on cytochrome P450c17 α and/or an increased sensitivity of adrenal to ACTH.

At the hepatic level, insulin inhibits the synthesis of the sex hormone-binding globulin, thereby increasing the amount of free androgens and consequently the peripheral androgen action. Insulin also inhibits the synthesis of IGF binding protein 1, leading to the increased bioavailability of IGF-1 and -2 [2]. Overall, these effects lead to an increased synthesis of androgens by the adrenal and ovarian thecal cells as well as an increased peripheral bioavailability of androgens and, therefore, to a condition of hyperandrogenism.

Finally, at the ovarian level, insulin directly acts on the granulosa cells of small follicles leading to premature granulosa terminal differentiation and the arrest of follicular growth. This effect in association with the insulin-mediated reduction in ovarian efficacy of gonadotropins and the increase in intraovarian androgen levels may cause premature follicular atresia and antral follicular arrest. This can subsequently lead to the collapse of small antral follicles into the ovarian stroma, leading to stromal hypertrophy and the promotion of ovarian atresia, finally leading to the development of polycystic ovarian morphology and anovulation [2].

Androgen excess, on the other hand, can aggravate IR through key effects on some target tissues. In females, androgens impair adipogenesis by inhibiting the proliferation and differentiation of mesenchymal stem cells and preadipocytes [10] with a compensatory adipocyte hypertrophy, which could induce adipocyte dysfunction that manifests itself in

IR, intracellular stress and inflammation [11]. In fact, hypertrophic adipose tissue is insulin resistant, produces a high amount of FFAs, and secretes high levels of pro-inflammatory cytokines, particularly TNF-alpha and IL-6 and low levels of adiponectin [11]. Androgens also have a direct effect on adipose insulin sensitivity. In particular, testosterone (T) directly induces IR in female subcutaneous adipocytes in vitro, and inhibits insulin-stimulated glucose uptake by impairing the phosphorylation of protein kinase C via an androgen receptor-mediated mechanism [12]. In addition, an enhanced lipogenesis has been found in the omental adipocytes of obese hyperandrogenic females compared with obese non-hyperandrogenic controls [13, 14]. This thus highlights the possible role of androgens in promoting visceral adipose lipid accumulation in women if such androgens are at supraphysiological concentrations.

At the level of the skeletal muscle, if androgens in females are at supraphysiological levels, they impair insulin sensitivity by interfering with insulin signalling and by inducing changes in the myocyte morphology. These changes can include, for example, a decrease in insulin sensitive type I fibres, an increase in less sensitive type IIb fibres, a decrease in capillarization, and the inhibition of glycogen synthase expression and activity [15]. Therefore, hyperandrogenism in females aggravates IR by directly affecting both the adipose tissue and the skeletal muscle.

All these data support the presence of a significant bidirectional interaction between IR and hyperandrogenism in females.

Clinical Studies Highlighting the Association between Hyperandrogenism and Severe IR States

The association of hyperandrogenism with severe IR states has been described only in a few studies. One study highlighted the presence of oligomenorrhea and hyperandrogenism in 7 females affected by INSR defects [16]. Another described ovarian hyperandrogenism in 3 members of a family of carriers of a non-functional, heterozygous mutation in AKT2 [17]. Other studies have described the association of oligo-amenorrhea, hirsutism, and hyperandrogenemia with FPLD2 [18–21].

In our experience, PCOS secondary to partial congenital lipodystrophy is more common than is thought. In fact, referrals to our centre in the last 10 years have shown a prevalence of 1% of PCOS secondary to partial congenital lipodystrophy. Of the 1,200 patients visiting our out-patient clinic for symptoms of PCOS (oligo-amenorrhea, hirsutism, infertility), we found 18 cases with a partial lipodystrophic phenotype. Of these, twelve cases were affected by a partial congenital lipodystrophy. In detail, nine were affected by a heterozygous missense mutation in gene LMNA, one case was affected by a heterozygous missense mutation in gene PPARG, and 2 cases by a heterozygous missense mutation in gene PLIN1. No substantial clinical differences among the different forms of partial congenital lipodystrophy were observed. The clinical characteristics of these patients are reported in Table 2.

Table 2. Clinical and biochemical characteristics of a group of patients with PCOS secondary to severe insulin resistance associated with lipodystrophy visiting our out-patient clinic for the first time

Patient	Mutation	Main complaint	Age, years	BMI, kg/m ²	T, ng/m	FGlu, mg/day	Flns, μ U/mL	H	AN	High Tg	NAFLD	DM	HBP	CV events	PCOm
1	LMNA	Hirsutism	21	26	0.7	72	21.0	Y	Y	Y	N	N	N	N	Y
2	LMNA	Amenorrhea	15	25	1.2	80	33.3	Y	Y	Y	Y	N	N	N	Y
3	LMNA	Amenorrhea	22	23	0.3	83	26.8	Y	Y	Y	N	N	N	N	N
4	LMNA	Hirsutism	35	22	0.2	95	21.3	Y	Y	Y	N	N	N	N	Y
5	LMNA	Hirsutism	62	24	0.6	100	16.2	Y	Y	Y	Y	Y	Y	Y	N
6	LMNA	Hirsutism	59	26	0.8	101	94.0	Y	Y	Y	Y	Y	Y	Y	Y
7	LMNA	Hirsutism	31	26	0.5	92	30.2	Y	Y	Y	Y	N	N	N	Y
8	LMNA	Amenorrhea	34	24	0.2	74	20.9	Y	Y	Y	Y	N	N	N	Y
9	LMNA	Hirsutism	16	22	0.8	83	21.6	Y	Y	Y	N	N	N	N	Y
10	PLIN1	Amenorrhea	33	37	0.3	106	39.0	Y	Y	N	Y	N	N	N	Y
11	PLIN1	Hirsutism	22	23	0.3	90	33.0	Y	Y	Y	Y	Y	N	N	Y
12	PPAR γ	Oligomenorrhea	31	25	1.5	91	88.2	N	Y	Y	Y	N	Y	N	Y
14	Unknown	Amenorrhea	19	47	1.0	83	82.0	Y	Y	N	Y	N	N	N	Y
15	Unknown	Amenorrhea	23	23	0.2	256	15.4	Y	Y	Y	Y	Y	N	N	Y

BMI, body mass index; T, testosterone; FGlu, fasting glucose; Flns, fasting insulin; H, hirsutism; AN, acanthosis nigricans; Tg, triglycerides; NAFLD, non-alcoholic fatty liver disease; DM, diabetes; HBP, hypertension; CV, cardiovascular; PCOm, polycystic ovarian morphology; Y, yes; N, no.

Therapeutic Strategies for Hyperandrogenism Secondary to Severe IR

The identification of a form of hyperandrogenism secondary to severe IR is important in clinical practice because it frequently benefits from tailored therapies, including specific dietary management or caloric restriction in general [22], as well as specific insulin sensitizers, such as thiazolidinediones [18], and in some cases, metreleptin therapy [23, 24]. Dietary management is the most critical element of treating severe IR because it can have a dramatic beneficial effect on metabolic derangement and, therefore, on hyperandrogenism. This is particularly important in lipodystrophy where, however, the apparent leanness of patients frequently results in a failure of caregivers to place sufficient emphasis on dietary modifications. On the other hand, the use of low-fat, energy-balanced or sometimes hypocaloric diets in lipodystrophic patients is of great benefit because of the “offload” of adipose tissue. However, dietary management is particularly difficult in lipodystrophy because both absolute and relative leptin deficiencies, in generalized and partial lipodystrophy, respectively, lead to hyperphagia [25]. Given the importance of restricting energy intake, particularly in patients with unrestrained accumulation of adipose tissue, other weight loss therapies, including glucagon-like peptide-1 agonists and appetite suppressants, can have clinical benefits, and bariatric surgery may perhaps be helpful in severe cases [1].

Insulin-sensitizing agents also play an important role in the management of severe IR states; however, metformin is often ineffective or insufficiently effective and requires the addition of thiazolidinediones, which are peroxisome proliferator-activated receptor γ agonists. Thiazolidinediones may be beneficial not only due to the systemic insulin-sen-

sitizing action and consequent reduction of hyperinsulinemia but also due to a direct insulin-independent effect on the ovary with a consequent decrease in thecal cell steroidogenesis [26]. In addition, they are of particular benefit in partial lipodystrophy because they stimulate adipogenesis, thus providing extra fat depots [18].

In patients with lipodystrophy and low levels of serum leptin, recombinant leptin therapy may dramatically improve glycaemic control, dyslipidemia, and hepatic lipid accumulation [27] and also to some extent resolve menstrual dysfunctions and hyperandrogenism [23]. The patients that benefit most from this therapy are those with extremely low or undetectable serum leptin levels. Leptin replacement should therefore always be considered in patients with generalised lipodystrophy.

Conclusions

Clinicians who deal with hyperandrogenic disorders should be alerted to the forms that are secondary to severe IR states as they are not as uncommon as may be expected and may respond to tailored therapies. The diagnosis of these forms remains predominantly clinical by examining patients in their underwear, looking out for clinical hallmarks, and supported by biochemical biomarkers. Gene screening is necessary to corroborate the diagnosis of some of these forms but must be performed at the end of the diagnostic path. Further studies are needed to detail the phenotypic features, diagnostic procedures, and potential therapeutic approaches to these secondary forms of hyperandrogenic states.

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